GR

GRANTS SUPPORTED IN 1980

OCTOBER 1980 SAB MEETING

CTR Presentation, 12/11/80

WJ Gardner

Exposure of mice to fresh, mobile smoke / Microbiological Bases -

To be completed 1981 - no further studies contemplated

3 expts completed - 2 B1 reg cig - (10 mice)

1 - no effect on incidence of lung tumors in sonacept mice

2 - Comb ā cgns didn't change incidence / age of onset

2 Comb. ā BAP & benzo, benzene cig

3 - Exposure to benz & benzene cigs - To be completed June '81

DNA Damage in lung.

Exp to smoke did result in new lung cells, reduced DNA repair (reduced DNA synthesis)

Epidemiology

Kaiser - Permanente - Effects of smoking & quitting

Swedish twins - Lower ca incidence for lung & other sites for twins than gen. pop.

Angina -

Siegrist

Cardiovascular disease -

Ford - Smoking & fetal development alter hormones

Stone - Nicotine in large doses can interfere ô vascular aspects of fetal devel; but in smaller doses effects are minimal

Another investigator finds nic

Proposed program -

Evaluate effects of nic & smoke as well as other agents like alcohol

Multidisciplinary

Examine effects on successive generations

Budget should be reviewed in prep. for action at Annual mtg on Jan 30.

Research Review Committee

1.- Cotinine study (Spears)
Awaiting ok for Phase I
Determine if cotinine in air
If nicotine present in suff. concentrations
Similar looking for group to do the work

2- Riley proposal

3- Passive dosimeters. Are they appropriate devices for measuring smoke exposure?

4- Formaldehyde problem.

5- See research proposal from Jenkins to Spears -
Indicate whether PM willing investigate.

CANCER STUDIES SUPPORTED IN 1980 (FOR SAB MEETING, OCTOBER 1980)

CANCER AND POLYCYCLIC AROMATIC HYDROCARBONS: Animal Studies	Animal Studies Continued	CHEMICAL CARCINOGENS (Non-PAH) Animal Studies	CIGARETTE SMOKE: CONDENSATE:NICOTINE Animal Studies/TC/Enzymes/Hormones	NITROSOCOMPOUNDS (Mouse/Rabbit)	VIRUSES AND CANCER (Mouse/Rabbit/Human)	I. EFFECTS OF VITAMIN A AND ANALOGUES II. ANTI-INVASION FACTORS: PROTEASES ETC.	IMMUNE RESPONSES (Animal/Human)	IMMUNE RESPONSES (Animal/Human) Continued	HUMAN STUDIES (SEE EPIDEMIOLOGICAL SECTION)	HUMAN STUDIES (CONTINUED)		
I. Pulmonary Carcinoma Mouse Models: Genetics Arcos (#922AR2)* II. Relationships to Cytochrome P450 (Mouse Strains) (a) Inducers in Cigarette Smoke Gielen (#1072AR1) (b) Epoxide Hydratase and Dihydrodiol Dehydrogenase, in Respect to Inactivation of PAH Carcinogens Oesch (#1097B) (c) Genetics: Ecotropic Virus:Chemical Carcinogenesis J. Levy (#1011B) (d) AHH: DMN Demethylase Arcos (#922AR2)* (e) Metabolic Profiles 1. Wang (#1005RR2) 2. Gielen (#1072AR1) (f) Purification P450's Wang (#1005RR2) (g) Bladder Ca:Glucuronidase: Sulfatase in Congenic Mouse Strains B. Paigen (#1267R1)	III. PAH-Proximate Carcinogens (P450 Independent Pathways) 6. hydroxylase activities (mouse strains) and inhibition of carcinogenesis by naphthoquinones Meier (#1290) IV. PAH Binding Protein Busbee (#1263R1) V. Rodent/Human Lung Epithelial Cell Cultures: Model for PAH Transformation Freeman (#1203RR1) TERMINATES/ED ** 12/31/80 * 6/30/80	I. Nitrosamines 1. Meier (#951B) 2. Arcos (#922AR2)* II. Genetic Test of Glucuronidase in Bladder Ca-Bladder Carcinogens: Congenic, Inbred mouse strains B. Paigen (#1267R1)	I. Smoke:Condensate Fractions (a) DNA Repair Damage: Mutagenesis Genetics: T.C. Rasmussen (#973B) (b) DNA Damage Alkaline Elution Assay Henry/Kouri (#1241R1) (c) Transformation:Mutagenesis Benedict (#1027B)** (d) Freeman (#1203RR1) II. Cigarette Smoke and PAH Metabolism-(AHH Inducers) Gielen (#1072AR1) III. Nitric Oxide Activation of Guanylate Cyclase-(Cigarette Smoke, Hormones, Drugs) a. Murad (#1184R2) b. Broughler (#1304) IV. Nicotine and B(a)P on Normal and Ectopic Hormone Production (Cultured rat-pituitary cells and human bronchogenic Ca cells) Bimma (#1303)	Biological Effects a. Synergism with PAH in Pulmonary Carcinogenesis PAH-Nitrosamine Syncarcinogenesis (mouse) Arcos (#922AR2)* b. Transplacental Effects (mouse/rabbit) Meier (#951B)	I. Genetic Genetic and Viral Determinants of Chemical Carcinogenesis (mouse/TC) J. Levy (#1011B) II. Cancer Risk Lung/Diagnostic Frenkel (#1216R1)	I. Metaplasia a. Galactosyl Transferases Wolf (#1028C) b. Oral Carcinogenesis, Vitamin A and Retinoids Shklar (#1169RR1) II. Anti-Invasion Factors: Proteases etc. a. Local Regulations of Normal and Pathologic Invasion Kuettner (#1206R2)	I. Role of Macrophage a. Normal/Activated Macrophages Unanue (#1030AR1) b. Cigarette Smoke Exposure on Developmental Cellular and Molecular Aspects of Immune Response Berecovitz (#1045B) II. Suppressor T Cells Pierce (#1040A)* III. Pulmonary Carcinoma: Secretory Component of IgA Reynolds (#1127AR1) IV. Lymphoid Cell Homing and Function Gillette (#1163RA)* V. Bronchial Lymphocyte: Cigarette Smoke and Ig Production Lawrence (#1215R1) VI. Lymphocytes: Cell Surface Membranes/Immune System/Aging/Neoplasia (rats) Weda (#1287) VII. B(a)P Metabolism: (Specific Antibodies) Slor (#1329)	VIII. Tumor a. Immune Response at Tumor Site in Lung Carcinoma (human tissue) Joachim (#943B)*	I. Population at Risk a. Onco-fetal Gene Expression: IC/SCR:AHH (Pulmonary Ca) Guirgis (#1132RR2)* b. Genetics and Biomarkers of Smoking-Associated Cancers Lynch (#1291H) c. PAH Metabolism: GSH Transferase: (Established Lymphocyte lines) Gurtoo (#1253R1) d. Conjugations/Lung Ca Risk: Glucuronyl and Sulfotransferases Gessner (#1174R2) e. Secretory Component of IgA As Marker of Pulmonary Carcinoma (bronchoalveolar lavage fluid) Reynolds (#1127AR1) f. Bladder Cancer: Galactosyl Transferases: Vitamin A Wolf (#1028C) g. Lung Ca-Diagnostic Test/Virus/TC Fibroblasts Frenkel (#1216R1) II. PAH Binding Protein: Detoxification System: Busbee (#1263R1) III. Tumor Registry: Lung Ca Meigs (#1255)	IV. Model for PAH Transformation (TC: human lung Epithelial cultures) Freeman (#1203RR1) V. Nicotine and B(a)P Effects On Hormone Production (human bronchogenic Ca cells) Bimma (#1303) VI. Monitor formation also Removal B(a)P Adducts From DNA by Specific Antibodies (RIA/monoclonal ab's/genetics/smokers and non-smokers) Slor (#1329)		

1005045292

CARDIOVASCULAR STUDIES SUPPORTED IN 1980 (FOR SAB MEETING, OCTOBER, 1980)
(SEE ALSO - EPIDEMIOLOGICAL/PHARMACOLOGICAL SECTIONS)

BLOOD FLOW/PRESSURE (SMOKE: NICOTINE CO) (DOG/RAT AND HUMAN)	ARTERIOSCLEROSIS THROMBOSIS	PLATELETS	ANGIOTENSIN: PROSTAGLANDINS	HUMAN STUDIES ALLERGY	HUMAN STUDIES SMOKING-CORONARY HEART DISEASE
a. Nicotine-Induced Reflex Coronary Vasodilation (Conscious Dog) Vatner (#974BR2)	a. 7-Ketocholesterol Inhibition of Cholesterol Uptake: CO/ Cholesterol Metabolism of Arterial Wall Bing (#310D)	a. Endothelial Cell and Platelet Response to Cigarette Smoke, Nicotine and CO 1. Mason (#939BR1M) 2. Chao (#1162A)	a. Metabolic Activities of Pulmonary Endothelium: angiotensin I-II, Thromboxanes, Prostaglandins Ryan (#814BR2)	a. Tobacco Allergens Gleich (#1014BR1)	SEE EPIDEMIOLOGY
b. Direct Effects of Nicotine on Brain Circulation (dog) Vatner (#1326)	b. Endothelial Cells: Platelets 1. Mason (#939BR1M) 2. Chao (#1162A) 3. Lee (#1261)	b. Platelet Microtubule Assembly: Aggregation. Effects of Ligands (Nicotine) Lee (#1261R1)	b. Nicotine Inhibition of Prostaglandin Biotransformation Wennmalm (#1300)		
c. Cigarette Smoking in Normo and Hypertensive Subjects (BP, Renin, Aldosterone and Catecholamines) Baer (#1160R2)	c. Role of LCAT (Smokers/Non-Smokers) Soloff (#1201R1)*	c. Nicotine Inhibition of Prostaglandin Biotransformation (platelet-vascular endothelium interactions). Wennmalm (#1300)			
	d. Smoke Exposed Pigeons (blood lipids) Hojnacki (#1229MR1)	d. Platelet Derived Growth Factor Antoniades (#1332)			
	e. Oxygenated Sterols in Human Blood Vessels Le Quesne/ Werthessen (#1271M)				
	TERMINATES/ED * 6/30/80				

PULMONARY STUDIES SUPPORTED IN 1980 (FOR SAB MEETING, OCTOBER 1980)

EMPHYSEMA/BRONCHITIS RDS/INFLAMMATION DISEASES

I. Proteases: Antiproteases

a. Mechanisms:Biochem (Elastase, α_1AP):
1. Travis/Powers (#1135A)
2. Johnson (#1217R1)

b. Experimental Emphysema:Lung Lesions
1. Weinbaum (#901B)
2. Geokas (#1088A)

c. Susceptibility to COPD In Smokers
1. PMN-Elastase (α_2MG/α_1AP, anionic hydrophobic agents
Galdston (#1242R1)

2. Pancreatic Elastase Circulating Levels (RIA method) α_1AP
Geokas (#1088A)

d. Mechanisms:Biochem and Inhibitors of Proteases:
1. Synthetic Inhibitors:
Travis/Powers (#1135A)

2. Endogenous Inhibitors (lung)
Johnson (#1217R1)

3. Macrophage Protease Inhibitors
O'Donnel (#1245)

EMPHYSEMA/BRONCHITIS CONTINUED

e. Mechanisms:Inhibitors of α_1AP (Cigarette Smoke):
1. Janoff (#1143A)
2. Travis/Powers (#1135A)

II. Purification of Macrophage Elastase
O'Donnel (#1245)

III. Elastin Biosynthesis
Foster (#1179R2)

IV. Elastin Degradation: (Measurement by RIA)
Janoff (#1259)

V. Delivery of Synthetic Protease Inhibitors by Microspheres
Liener (#1214)*

ENVIRONMENTAL (Cigarette Smoke: Active/Passive)

I. Human Studies
a. Respiratory Disease In Infancy Development of Lung Disease in Adults
C. Hall (#1164R2)

b. Pulmonary Function: Adolescents-Parents Pulmonary and Smoking Histories
B. van den Berg (#1171R2)

c. Predisposition to COPD
M. Galdston (1242R1)

d. Airway Hyperreactivity (Ozone:Cigarette Smoke)
J. Nadel (#1311)

e. Alveolar Clearance Rate of Inert Particles:(Non-Invasive, Magnetic Technique).
A. Freedman (1321)

II. Animal Studies
a. Morphological and Metabolic (phospholipids:biochemistry)
Cigarette Smoke On Fetal and Perinatal Lung Development and Metabolism (Rat)
M. Hamosh (1130B)*

ENVIRONMENTAL CONTINUED

b. Airway Hyperreactivity (Canine): (Ozone:Cigarette Smoke)
J. Nadel (#1311)

c. Ozone on Airway Mast Cells Cigarette Smoke (Canine)
(On Neurohumoral modulation/histamine release: cyclic AMP/GMP).
W. Gold (#1327)

SPECIAL MORPHOLOGICAL SPECIAL FUNCTIONS OF LUNG

I. Endocrine Functions

a. Endocrine-Like Cells In Airways: (Effects of Hypoxia and CO)
Echt (#1244A)

b. APUD CELLS: (Endocrine like cells of lung, and their local neurohormonal control mechanisms)
1. Will (#1036AR2)
2. Kleinerman (#1190)*

c. Metabolic Activities of Pulmonary Endothelium:(Angiotensin I-II: Thromboxanes/Prostaglandins etc.)
Ryan (#814BR2)

d. Mast Cells:
W. Gold (#1327)

IMMUNE MECHANISMS IMMUNOGLOBULIN PRODUCTION: HYPERSENSITIVITY: ALLERGY (CHRONIC BRONCHITIS)

I. Tobacco Antigen
Gleich (#1014BR1)

II. Cigarette Smoking and Ig Production: Human Bronchial lymphocyte.
Lawrence (#1215R1)

TERMINATES/ED

* 6/30/80

MACROPHAGE STUDIES

I. Immunological

a. Lawrence (#1215R1)
b. Springer (#1307)
c. Herscowitz (#1045B)
d. Unanue (#1030AR1)

II. Proteases

a. Travis (#1135A)
b. Weinbaum (#901B)
c. O'Donnel (#1245)

III. Contractile Proteins: Plasma Membrane (Rabbit)
Stossel (#1116A)

IV. Factors in Pulmonary Inflammation
Cochrane (#764HR1)

PSYCHOPHARMACOLOGY AND PHARMACOLOGICAL STUDIES SUPPORTED IN 1980 (FOR SAB MEETING, OCTOBER 1980)

HUMAN STUDIES (Cigarette Smoking)

a. Behavioral Effects: a) Non-Smokers and Exposure to Smoking, b) Smoking-Deprivation
Heimstra (#1081AR1)

b. Influence of Pregnancy on Metab./Excretion of Nicotine (urine/amniotic fluid/breast milk/fetal tissue/blood)
Gorrod (#1194R1)*

TERMINATES/ED

* 6/30/80

ANIMAL STUDIES (Behavioral/Biochemical)

I. Genetics/Nicotine/Smoke

a. Neurochemical and Behavioral Effects of Nicotine and Alcohol
Collins (#1204R2)

b. Nicotine: Isolated Perfused Mouse Brain Biogenic Amines
Erwin (#1251A)

c. Cigarette Smoke:Nicotine Alcohol
Petersen (#1243R1)

ANIMAL STUDIES (Metabolic)

I. Nicotine/Cotinine

a. Actions of Nicotine on Serum Pancreatic Elastase Levels:(Dogs)
Geokas (#1088A)

b. Effects on Catecholamine and Neuroendocrines:
Fuxe (#1223R1)

c. Nicotine Isolated Perfused Mouse Brain. Biogenic Amines
Erwin (#1251A)

II. Tobacco Smoke/Nicotine/CO

a. Action on Acetylcholine System (Human Placenta)
Rama Sastry (949B)

b. Brain-Development: Nicotine/Smoke Effects
1. Lewis (#1187MR1)
2. Lajtha (#1234A)

c. Nicotine Metab./Pregnancy
Gorrod (#1194R1)*

ANIMAL STUDIES (Metabolic) CONTINUED

III. Guanylate Cyclase:Nitric Oxide Effects

a. Cyclic GMP/Free Radicals
Braughler (#1304)

b. Murad (#1186R2)

ANIMAL STUDIES (Nicotine Receptors/Binding) Sites and Absorption)

I. Central Nicotine Receptor

a. Tometsko (#1161R2)
b. Collins (#1204R2)

II. Neural Tissue Receptors-Genetics (Drosophila Melanogaster Mutants)
Hall, L. (#1126AR1)

III. Receptors Spectroscopic Studies
D. Nelson (#1230R1)

IV. Receptors: Blood Cells
Hoss (#1235R1)

NICOTINE-METABOLITES/DERIVATIVES

I. RIA For Nicotine Metabolites

a. RIA
Castro (#884C)

b. Synthesis of Antigens
McKennis (#1054A)

II. Nicotine Derivatives (Synthesis for Receptor Studies)
Tometsko (#1161R2)

III. Nicotine-Metab./Excretion: Pregnancy Influence of
Gorrod (#1194R1)*

IV. Nicotine: Delivery Systems: Metabolism
Erickson (#1208A)

MISCELLANEOUS STUDIES SUPPORTED IN 1980 (FOR SAB MEETING, OCTOBER 1980)

REPRODUCTION

I. Human

Nicotine Effects
(Human Placenta)

Acetylcholine System:
Rama Sastry (#949B)

II. Animal

(a) Nicotine: CO
(Cell Cleavage:Implantation Gestation)
Mitchell (#1012AR2)*

(b) Brain Development: Offspring
(NICOTINE/TOBACCO SMOKE)
1. Lewis (#1187MR1)
2. Lajtha (#1234A)

IMMUNOLOGY
(See Cancer Studies)

I. Basic Studies

(a) Biology of Supressor-T Cells
Pierce (#1040A)*

(b) Normal and Activated Macrophages
Unanue (#1030AR1)

(c) Lung Immunology
Lawrence (#1215R1)

(d) Lymphocytes:Cell Surface Membranes/Proteins Cytoskeleton, In Aging and Cancer(Rat)
(cell recognition:cell surface receptors)
Woda (#1287)

II. Macrophage

(a) Normal-Activated
Unanue (#1030AR1)

(b) Cigarette Smoke: Developmental cellular/molecular aspects of immune response
Herscowitz (#1045B)

IMMUNOLOGY
(CONTINUED)

(c) Macrophage Subpopulations:Differentiation:Monoclonal Antibodies.
(Cell Surface Antigens).
Springer (#1307)

III. Lymphoid Cell Homing and Function: (effects of tobacco byproducts)
Gillette (#1163MA)*

IV. Allergy (Tobacco Antigen)
Gleich (#1014BR1)

TERMINATES/ED

* 6/30/80

EPIDEMIOLOGICAL STUDIES SUPPORTED IN 1980 (FOR SAB MEETING, OCTOBER 1980)

(HEALTH/DISEASE/MORTALITY: RELATION TO SMOKING/ENVIRONMENTAL)

SMOKING: NON-TWIN STUDIES	SMOKING: TWIN STUDIES	PROTEASES: ANTIPROTEASES (See Pulmonary Studies)	CANCER
1. Epidemiological Pulmonary Function in Adolescents:Parents Pulmonary Pathologies and Smoking Histories van den Berg (#1171R2)	(a) Swedish Twin Registry Friberg (#1136A) (b) Finnish Twin Registry Rantasalo (#953AR2) (c) Susceptibility Indices for Lung Cancer:Immunochemical and Other Markers Guirgis (#1132MR2)*	I. Smoking:Non-Smoking:Blood Levels-Pancreatic Elastase (RIA). Geokas (#1088A) II. Cigarette Smoking-COPD: Galdston (#1242R1)	I. Familial Aggregations. Genetics and Biomarkers of Smoking-Associated Cancers (a) Lynch (#1291M) (b) Guirgis (#1132MR2)* (c) Gessner (#1174R2) II. Lung Cancer: PAH Metabolism Gurtoo (#1253R1) III. Bladder Cancer Wolf (#1208C)

Terminates/ed
* 12/31/80
** 6/30/80
*** 4/30/80

1005045298